REMARKS

Claims 37-39 are pending in the application. Claims 37 and 38 are rejected and claim 39 is allowed.

Claims 37 and 38 remain rejected as allegedly unpatentable over Bonjouklian, *et al.* (U.S. Patent No. 5,378,725, referred to herein as "Bonjouklian") in view of Arnold, *et al.* (*Genes, Chromosomes, and Cancer* 16:46-54, 1996, referred to herein as "Arnold") and Volinia, *et al.* (*Genomics* 24:472-477, 1994, referred to herein as "Volinia") and further in view of Xiao, *et al.* (*International Journal of Oncology* 6:405-411, 1995, referred to herein as "Xiao") or alternatively, Skorski, *et al.* (*Blood* 86:726-736, 1995, referred to herein as "Skorski").

Applicants thank the Examiner for the telephonic interview on April 8, 2005 in which the remaining rejection was discussed. The Examiner reiterated the position that the claims are obvious because the cited Xiao *et al.* and Skorski *et al.* references showed that the PI3 kinase inhibitor wortmannin inhibited proliferation of human gastric cancer cells and human leukemia cells, respectively, thereby creating a reasonable expectation of success that wortmannin would be effective inhibiting proliferation of ovarian cancer cells, including those determined to have an amplification at 3q26.3. The Examiner further clarified that Applicants' arguments should be supported by evidence in the way of supporting publications or declarations.

Applicants traverse the rejection for reasons of record. As previously noted, the current invention relates to inhibition of the pathologic proliferation of ovarian cancer cells as set forth in the claims. Xiao *et al* and Skorski *et al.*, however, describe experiments conducted with non-ovarian cancer cells, which experiments were exclusively performed *in vitro*. Skorksi *et al.* investigated the potential role of PI 3 kinase in the bcr/abl tyrosine kinase pathway in leukemia cell *in vitro*. Xiao *et al.* examined the potential role of tyrosine phosphorylation and PI3 kinase on the growth of gastric cancer cell lines *in vitro*. Further, neither publication relates to tumor cells having an amplification of 3q26.3. Indeed, both references focus on PI 3 kinase 85-kDa subunit expression, not p110 subunit (encoded by PIK3CA) expression.

The art prior to Applicants' invention teaches that the results of *in vitro* studies of particular cancer cells, such as the studies described by Xiao e*t al* and Skorksi *et al.*, cannot necessarily be extrapolated to apply to other cancer cells *in vitro* or to treatment of cancer cells *in vivo*. Schultz *et al.*, *Anticancer Res.* 15:1135-1139, 1995, provided in the supplemental IDS submitted herewith, evaluated the cytotoxic effects of wortmannin on various tumor cell lines *in vitro* (*see, e.g.,* Table 1 on page 1136). They also studied the antitumor effects in mouse tumors (*e.g.,* Table III on page 1136) *in vivo* and human carcinoma xenografts (*e.g.,* Table V, page 1137) *in vivo*. Their experiments indicated that *in vivo* antitumor activity did not correlate with *in vitro* sensitivity to wortmannin (last sentence of the abstract) in the cell lines that they tested. In fact, Schultz *et al* found that "*[I]n vivo* antitumor activity was not observed with two human cell lines (GC3 colon carcinoma and IGROV1 ovarian carcinoma) having the greatest sensitivity to wortmannin cytotoxicity *in vitro* (contrast Table V to Table 1)." (page 1138, lines 12-15 of the last paragraph on column 1). Thus, the teachings of Schultz *et al.* indicate that the findings of Xiao *et al.* and Skorski *et al.* in the *in vitro* gastric cancer and leukemia cell models do not provide a reasonable expectation that wortmannin would be effective for inhibition of the pathological proliferation of ovarian cancer cells.

The findings of Schultz *et al.* additionally indicate that not all ovarian cancer cells may be sensitive to wortmannin. In the instant application, Applicants have shown that PI3 kinase inhibitors <u>are</u> effective inhibitors of the pathological proliferation of target ovarian cancer cells set forth in the claims. The Examiner contends that it would have been obvious that Bonjouklian's suggestion to treat PI3-kinase-dependent tumors, including ovarian cancer, with wortmannin would include ovarian cancer cells that had regions of amplification of 3q26 as taught by Arnold and, based on Volinia's publication that PIK3CA is found in 3q26.3, one of skill would have been taught that such treatments would include cells in which 3q26.3 was amplified. However, the combination of art is deficient at arriving at the claimed invention. As Applicants have previously noted, it does not provide a teaching or suggestion that 3q26.3 specifically is amplified in ovarian cancer cells. Furthermore, Bonjouklian is silent as to what constitutes a PI3-kianse-dependent ovarian tumor. The combination of art therefore does not

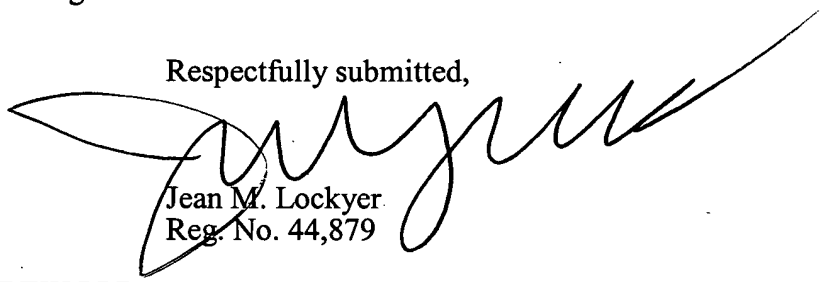
lead the artisan to Applicants' invention. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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